IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

ACTELION PHARMACEUTICALS LTD., *Plaintiff,* v. MYLAN PHARMACEUTICALS INC., *Defendant.*	Civil Action No. 1:20-CV-00110-JPB Hon. John P. Bailey

DEFENDANT MYLAN PHARMACEUTICALS INC.'S POST APPEAL CLAIM CONSTRUCTION BRIEF REGARDING EXTRINSIC EVIDENCE

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INTRODUCTION

The Federal Circuit has remanded this case to determine the proper construction of the term "pH of 13 or higher" as used in the'802 and '227 patents in light of the extrinsic evidence.[1] As used in the claims, "pH of 13" would be readily understood by a skilled artisan to mean 13.0. By focusing the analysis to the extrinsic evidence, the Federal Circuit all but blessed this interpretation. Indeed, in each one of three originally cited references, the evidence shows that a pH shown as a whole number is always equivalent to a concentration of hydrogen ions with one significant figure. It necessarily follows that every whole-number pH implies a significant figure of ".0": "pH of 13" is "pH of 13.0." But, there is more. Additional extrinsic evidence squarely addresses the issue of how precisely pH is measured and what margin of error a skilled artisan would expect. All told, the extrinsic evidence supports a construction setting a pH floor at 13.0, with, at most, minimal variance (plus or minus 0.02 pH units) to account for measurement error.

The Federal Circuit's decision found the intrinsic evidence equivocal and indeterminate. But it recognized that "pH" has a specific meaning to skilled artisans, which carries a definite "precision of measurement" tied to the number of significant figures in a pH value. It cited three textbooks for the undisputed scientific proposition that "the number of significant figures in the concentration equals the number of digits to the right of the decimal point in the logarithm [pH value]." The Federal Circuit then observed that this extrinsic evidence, though not considered below, "appear[ed] highly relevant to how a person of ordinary skill would understand the language 'a pH of 13.'" Because it could not engage in fact-finding, the Federal Circuit vacated and remanded for this Court to construe "a pH of 13 or higher" in light of this "highly relevant" evidence in the first instance.

[1] The Federal Circuit's opinion issued on November 6, 2023; the mandate has yet to issue.

While the Federal Circuit was constrained from adopting Mylan's construction outright, it framed the appropriate question for this Court: Can a pH value "be measured precisely—and to what degree?" Actelion's own extrinsic evidence answers those questions in favor of Mylan's construction. Skilled artisans measure pH precisely down to at least the hundredth of the unit (two decimal places). And when pH is expressed as a whole number (*i.e.*, as an integer), skilled artisans understand that it necessarily implies at least one significant digit to the right of the decimal place; "pH of 13" is "pH of 13.0." These conclusions all follow because pH is shorthand to express the actual quantity of what a skilled artisan is ultimately measuring—the concentration of hydrogen ions in an aqueous solution. A pH value simplifies the very small numbers (and very wide range) involved in the potential hydrogen ion concentration by putting *magnitude* on the left side of the decimal point and the *certainty* for purposes of the measurement on the right. Notably, this means the "significant figures" of a pH value are only the digits to the right of the decimal point.

The evidence shows this is how skilled artisans actually measure pH in practice. Standard pH meters are used, which allow for a degree of precision to at least two digits to the right of the decimal place. Pharmaceutical industry standards as of the priority date required the use of a pH meter accurate "***within 0.02 pH***." The claim language, intrinsic evidence, and extrinsic evidence establish two facts: a skilled artisan will always understand that a round-number integer pH value implies at least one significant figure (13.0); and a skilled artisan will understand that, *if* a margin of error is required, it will be on the order of pH 0.02 in either direction—*i.e.*, "pH of 13 or higher" means "pH of 12.98 or higher."[2] Thus, the Federal Circuit was correct in noting "the nature of measuring a pH value might nonetheless reasonably require a margin of error." But that margin of

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[2] As discussed below, the U.S. National Institute of Standards and Technology endorses an even narrower margin of 0.01—*i.e.*, "pH of 13" would equate to "12.99 to 13.01." The Court may take judicial notice of NIST standards pursuant to Federal Rule of Evidence 201.

error would never be 0.5, allowing a drop down to a pH of *12.5*, as Actelion argued. Instead, the lowest claimed value could only be "12.95"—which results only if one accepts Actelion's flawed assertion that general rounding principles trump pharmaceutical industry standards tied directly to pH measurement protocols.

The Federal Circuit recognized the flaws in Actelion's assertion that the ordinary meaning of "pH of 13" is "pH of 12.5 to 13.4" because "pH of 13" has two significant figures. Indeed, as the Federal Circuit's decision highlighted, Actelion's own evidence confirms a "pH of 13" *would not* round because it has *zero* significant figures. To avoid the implications of its own argument, Actelion may try to pivot to a second, more convoluted theory which the district court did not credit the first time around. Actelion's fundamentally results-oriented "orders-of-magnitude" theory is indefensible, atextual, and impermissibly abstract, Moreover, it cannot be squared with the Federal Circuit's opinion. This Court should adopt Mylan's construction consistent with the science and real-world practice of skilled artisans, bolstered by the Federal Circuit's recognition of those realities as disclosed in the extrinsic evidence.

In sum, the only permissible constructions of "pH of 13 or higher" are (1) "a pH of 13, but not less than 13, or higher," such that any pH values below 13 are not included; or (2) encompassing a margin of error based on the necessarily implied significant figure: "a pH of 12.98 or higher," consistent with industry standards, or "a pH of 12.95 or higher," consistent with principles of significant-figure-based rounding.

BACKGROUND

A. The Intrinsic Evidence

The patents-in-suit claim formulations of epoprostenol, a naturally occurring substance used to treat cardio obstructive pulmonary disease.[3] *See* Dkt. Nos. 62-1, 62-2.[4] It was well-known as of the priority date that epoprostenol is chemically unstable, which places limits on long-term storage and use. It was also known that epoprostenol stability is "pH dependent." Dkt. No. 62-1 (2:65-66). The '802 and '227 patents describe stable, highly basic formulations of epoprostenol, as well as the method for preparing them and maintaining stability. Critical to achieving this result is a "bulk solution" of epoprostenol adjusted to an extraordinarily high pH value prior to lyophilization (freeze drying). The '802 and '227 patents claim bulk solutions of epoprostenol with "a pH of 13 or higher." Dkt. No. 62-1 (10:62-18:54). Construction of this term impacts the claims and defense with respect to all asserted claims in this case.

As the Federal Circuit recognized, the "claim language, 'a pH of 13 or higher,' is a range with a specified lower limit." *Actelion Pharms. LTD v. Mylan Pharms. Inc.*, 85 F.4th 1167, 2023 WL 7289417, at * 3 (Fed. Cir. Nov. 6, 2023). Significantly, "the claims do not recite just any measurement of 13 or higher; rather they are directed to a ***pH*** of 13 or higher." *Id.* at *4 (emphasis added). "Unlike other claim terms, the disputed claim term lacks approximation language like 'about.'" *Id.*

The specification establishes that the inventor understood "pH of 13" referred to a specific, measurable pH value. When setting forth the ingredients and preparation of the claimed bulk solution, for example, it explains that the "pH of the bulk solution is preferably adjusted to about

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[3] U.S. Patent Nos. 8,318,802 (the '802 patent) and 8,598,227 (the '227 patent).

[4] For convenience, Mylan cites the patents and prosecution history as previously docketed in this matter. The specifications of the '802 and '227 patents are materially identical.

12.5-13.5, most preferably 13." Dkt. 62-1 (5:40-43). Indeed, the specification equates "13.0" with "13." It describes Table 8 as displaying formulations "with the pH of bulk solution for lyophilization adjusted between 10.5 and 13.0," Dkt. 62-1 (10:62-64), and that table shows nine formulations with bulk solution pH of "13," without a decimal or trailing zero. Dkt. 62-1 (Table 8). Because the results showed better stability "at pH 13 compared to lower pH samples," Dkt. 62-1 (11:54-56), the inventor prepared additional batches "with the pH of bulk solution adjusted to 13." Dkt. 62-1 (11:58-60). No pH value less than 13 produced a stable formulation. Nothing in the specification, in other words, suggests that the inventor intended "pH of 13 or higher" to refer to "pH of 12.5 or higher."

The prosecution history reinforces this conclusion. First, it contains *direct evidence* that the pH "13" values in Table 8 refer to pH "13.0"—the March 20, 2006 provisional application[5] recites the pH of those compositions as "13.0":

> EPP-7: Epoprostenol sodium - 0.5mg, arginine - 50mg, pH - 13.0
>
> EPP-9: Epoprostenol sodium - 0.5mg, arginine - 50mg, lactose - 50mg, pH of bulk solution adjusted to 13.0 with 0.1N NaOH (1ml of 0.1N NaOH)
>
> EPP-10: Epoprostenol sodium - 0.5mg, arginine - 50mg, HES - 50mg, pH of bulk solution adjusted to 13.0 with 0.1N NaOH (1ml of 0.1N NaOH)
>
> EPP-12: Epoprostenol sodium - 0.5mg, sodium carbonate - 100mg, pH of bulk solution adjusted to 13.0 with 0.1N NaOH (1ml of 0.1N NaOH)
>
> EPP-13: Epoprostenol sodium - 0.5mg, hydroxyethyl starch (HES) – 50 mg, pH of bulk solution adjusted to 13.0 with 0.1N NaOH (1ml of 0.1N NaOH)

It also directly equates "pH of 13" and "pH 13.0" (boxes added):

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[5] *See* Patent Application 60/783,429, Specification at 3, 10 *available at* https://patentcenter.uspto.gov/applications/60783429/ifw/docs. The file history is publicly available and subject to judicial notice. *See, e.g., Standard Havens Prod., Inc. v. Gencor Indus., Inc.*, 897 F.2d 511, 514 n.3 (Fed. Cir. 1990).

24 hours. We have also assessed the stability of diluted solution containing epoprostenol (0.1 mg/ml) and arginine 10 mg/ml at pH 13. The stability data is summarized in the table 11 below.

Table 11: Solution stability of Epoprostenol (0.1 mg/ml) in presence of 10 mg/ml of arginine, pH 13.0, at 29±1°C

More generally, the prosecution history reveals a process of repeated amendments and rejections specifically aimed at narrowing the claimed bulk solution pH range. The inventor narrowed the term from "greater than 11" to "greater than 12," and finally, in response to the Examiner's disapproval of a claim encompassing pH values under 13, amended it to "13 or higher." *See generally* Dkt. 62-4. The Examiner, in other words, drew the line between obviousness and patentability between pH of "12" (which showed no surprising stability) and pH of "13" (which showed surprising stability)—the Examiner did not draw the line between 12.4 and 12.5.

B. The District Court and Federal Circuit Opinions.

Mylan has consistently advocated a claim construction most consistent with the intrinsic record—"pH of 13 or higher" refers to a pH of *exactly* 13 or higher, such that pH values below 13 are not encompassed by the claim. In the alternative, Mylan proposed that if a margin of measurement error were needed, and accepting Actelion's assumptions, it would expand the claimed range *at most* to encompass a pH of 12.95. In contrast, Actelion asserted the "ordinary meaning" of "pH of 13" would encompass values that round up or down to the integer "13." The District Court originally adopted Actelion's position, holding that "pH of 13" was expressed with two significant figures and, "under its conventional significant figure meaning," the number 13 "would ordinarily encompass those values that round up or down to 13, 12.5 to 13.4." *Actelion Pharms. Ltd. v. Mylan Pharms., Inc.*, No. 1:20CV110, 2022 WL 446788, at *5 (N.D.W. Va. Feb. 14, 2022).

The Federal Circuit vacated the judgment, signaling that the construction adopted cannot be squared with the record. The issue on appeal was "the meaning of 'a pH of 13 or higher,'" and "[m]ore specifically . . . what the significant digits are for 'a pH of 13.'" *Actelion*, 2023 WL 7289417 at *1. Actelion argued that "the district court correctly construed the claim term as including rounding to the ones place, noting that 'a numerical value includes rounding based on the inventor's selection of significant figures in the claims where the intrinsic record does not indicate otherwise.'" *Id.* at *3. Mylan, by contrast, argued "that the claim term creates a floor at 13, beneath which the pH cannot fall." *Id.* The Circuit also twice highlighted Mylan's *alternative* argument "that[,] if a margin of error for a pH of 13 is needed, a pH of 13 would involve rounding to the hundredths place, encompassing 12.995–13.004." *Id.*; *see also id.* at *2 ("[Mylan] explained that if the district court were inclined to include measurement errors for a pH of 13, Actelion's three chemical textbooks support a narrower range of 12.995–13.004.").

The Circuit deemed the "intrinsic evidence [to be] rather equivocal." *Id.* at *3. "At the same time," it observed, "the extrinsic evidence relied on by the parties—but unconsidered by the district court—appears highly relevant to how a person of ordinary skill would understand the language 'a pH of 13.'" *Id.* Although Actelion contended that "pH of 13" had two significant figures and therefore rounded to the ones place, textbooks of record agreed that, for a pH, "only the digits to the right of the decimal point" are significant figures. *Id.* at *2 (quotation marks omitted). It was therefore necessary to remand for this Court to consider, using extrinsic evidence, "how a person of ordinary skill in the art would view the significant digits for a pH value," and thereby reconsider and decide the correct construction of "pH of 13 or higher." *Id.* at *1.

The Federal Circuit's opinion provided several principles to guide and cabin the inquiry on remand. *First*, the Circuit confirmed the correct claim construction inquiry does not involve

abstract numbers or principles of mathematics. Instead, it must consider how precisely the pH value of 13 can be measured by the skilled artisan. The claims, it explained, "recite [a] *measurement* of 13 or higher." *Id.* at *4. And they "do not recite just any measurement of 13 or higher; rather they are directed to a pH of 13 or higher." *Id.* Hence, "the district court should consider whether a pH of 13 carries any meaning to a person of ordinary skill in the art as regards *precision of measurement*, significant digits, or rounding." *Id.* (emphasis added).

Second, the Circuit explained that the claim language "pH of 13 or higher" had two reasonable constructions. Although Mylan had contended that the absence of "about" or "approximately" in front of the term "13" indicated no rounding was intended, the Circuit did not find "the absence of approximation language" to be "dispositive." *Id.* Rather, it recognized that the claim language "pH of 13 or higher" has one of two "equally plausible" interpretations: either the "absence of approximation language . . . suggest[s] no approximation" for "pH of 13," or "the nature of *measuring* a pH value . . . [] reasonably require[s] a *margin of error*." *Id.* (emphasis added). Importantly, in describing this latter option, the Federal Circuit used the same term as Mylan's alternative argument—one it advanced if "a margin of error for a pH of 13 is needed." *Id.* at *4. The Circuit "le[ft] for the district court to determine in the first instance" whether "a pH value can be measured precisely—and to what degree." *Id.* at *4 n.2.

Third, the Circuit concluded that the specification and prosecution history were not, by themselves, sufficient to determine the correct construction. It noted the "specification seems to equate a pH of '13.0' to that of '13." *Id.* at *5. It "may be so" that "the inventor equated a pH of '13' with '13.0,'" the Circuit observed. *Id.* But the specification alone could not conclusively show it, because it "uses both '13' and '13.0'—and various degrees of precision for pH values generally—throughout." *Id.* at *5. For its part, the prosecution history showed that the pH values

in specification Tables 8 and 9 were decisive in allowing the inventor to demonstrate unexpected results for pH of 13. *See id.* This, too, was inconclusive; "Tables 8 and 9 simply do not compare compositions with pH values of 13 to those with a pH between 12 and 13." *Id.* The Circuit did not, however, rule out the possibility that the extrinsic evidence could confirm or reinforce an understanding of the intrinsic record consistent with Mylan's position.

LEGAL STANDARD

The Federal Circuit remanded this case for this Court to consider extrinsic evidence. "Extrinsic evidence is that evidence which is external to the patent and file history, such as expert testimony, inventor testimony, dictionaries, and technical treatises and articles." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996). "[E]xtrinsic evidence in general, and expert testimony in particular, may be used only to help the court come to the proper understanding of the claims; it may not be used to vary or contradict the claim language." *Id.* "When, after considering the extrinsic evidence, the court finally arrives at an understanding of the language as used in the patent and prosecution history, the court must then pronounce as a matter of law the meaning of that language." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 981 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

ARGUMENT

I. The Extrinsic Evidence Confirms "a pH of 13" Means a pH of Precisely 13, With Only Minimal Deviation for Measuring Error if Any is Required.

The correct claim construction of "pH of 13 or higher" follows from the scientific nature of a pH value, the instruments used to measure pH, and the standards of precision skilled artisans practicing applied pharmaceutical chemistry are required and expect to observe.[6] None of these

[6] The Court can and should rule in Mylan's favor based solely upon the three textbooks Actelion offered during the first round of claim-construction briefing. Nonetheless, Mylan provides the declaration of Dr. William Hensler in support of the principles laid out in those textbooks,

things have changed since the priority date of the patent—February 3, 2006. They were true then and are true now. The extrinsic evidence establishes that skilled artisans understood that pH values expressed as whole numbers always have *at least one* significant figure to the right of the decimal point, whether explicit or implied. This means "pH of 13 or higher" is conceptually equivalent to "pH of 13.0 or higher" because it necessarily reflects a measured pH value with at least one significant figure. Precision is always present. From there, a skilled artisan applies the standards and protocols of pharmaceutical science and reaches the correct construction; it includes either *no* values below 13 or, to account for instrument error, extends to pH of 12.98 using industry standards.

A. Skilled Artisans Understand All Whole-Number pH Values to Have at Least One Significant Digit to the Right of the Decimal.

pH is a "simple system for communicating concentrations" of hydrogen ions in an aqueous solution. Hensler Decl. Ex. B at 540; *see also* Hensler Decl. Ex. D at 775.[7] Without pH, measuring and analyzing the acidity or alkalinity of a solution would be a mess of zeros or base-10 exponents. "The concentration of hydronium ions ranges from about 10 mol/L for a concentrated strong acid to about 10^{-15} mol/L for a concentrated strong base. This wide range of concentrations, and the negative powers of 10, are not very convenient to work with." Hensler Decl. Ex. C at 386. "The concept of pH makes working with very small values, such as 0.000 000 000 000 01, much easier." *Id.* For example, that concentration has thirteen zeros after the decimal point before even reaching the first nonzero digit of "1." It is only slightly less cumbersome to express that number in

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explaining how a skilled artisan would understand and apply these principles to the claim language. All of this is consistent with Dr. Hensler's expert report previously produced to Actelion, upon which Actelion has also deposed him.

[7] "Hensler Decl." refers to the Declaration of William T. Hensler, Ph. D. in Support of Mylan's Claim Construction Briefing, attached hereto as Exhibit 1. The extrinsic evidence in this case, including the three Chemistry textbooks, is attached as lettered exhibits to the Hensler Declaration.

exponential notation: "1 x 10^{-13}." The concept of pH addresses this problem. It is calculated from the negative logarithm of the base ten of the hydrogen ion concentration: pH= $-\log[H^+_{(aq)}]$. Hensler Decl. Ex. B at 540. So, to calculate the pH of neutral water:

$$\begin{aligned} \therefore \text{pH} &= -\log\,[H_3O^+] \\ &= -\log\,(1.0 \times 10^{-7}) \\ &= -(-7.00) \\ &= 7.00 \end{aligned}$$

Hensler Decl. Ex. C at 387.

As the Federal Circuit pointed out, *see Actelion*, 2023 WL 7289417, at *1-2, understanding how the component parts of pH work and what they mean for a skilled artisan is critical to the correct claim construction. As Kessel explains, "the digits preceding the decimal point in a pH value are determined by the digits in the exponent of the given hydrogen ion concentration. These digits serve to locate the position of the decimal point in the concentration value and have *no connection with the certainty of the value*." Hensler Decl. Ex. B at 541 (emphasis added). So, if the digit to the left of the decimal is 7, that corresponds to 10^{-7}. Standing alone, though, "10^{-7}" does not denote a concentration of ions, let alone a pH value. It just expresses an order of magnitude. It is an abstraction; a power of ten signifying the number of zeros. It is not a *measurement* of anything. Hensler Decl. ¶¶ 27, 60.

A power of ten is a concept, not a measurement. As the Federal Circuit recognized, however, the point of pH is to *measure* hydrogen ion concentration. 2023 WL 7289417, at *4. All measurements must have some degree of "certainty." That is where significant figures come in. In any pH, "the number of digits following the decimal point in the pH value is equal to the number of significant digits in the hydrogen ion concentration. For example, a hydrogen ion concentration of 2.7 X 10^{-3} mol/L corresponds to a pH of 2.57. (Two significant digits in the value for $[H^+_{(aq)}]$

means we should give the pH value to two decimal places.)" Hensler Decl. Ex. B at 541.[8] Because the digits to the left of the decimal denote a power of ten, only the digits to the *right* of the decimal in a pH value are considered significant: "*[T]he number of significant figures in the concentration equals the number of digits to the right of the decimal point in the logarithm[.]*" Hensler Decl. Ex. D at 775 (emphasis added); *see id.* ("5.4 x 10^{-4} M has two significant figures, so its negative logarithm, 3.27, has two digits to the right of the decimal point."); Hensler Decl. Ex. C at 387 ("How do you determine the number of significant digits in a pH? You count only the digits to the right of the decimal point.").[9]

The upshot is that all pH values given as a whole number necessarily carry at least one digit to the right of the decimal. If not, the pH value would have *zero* significant figures—that is, no "precision" whatsoever. *See* Hensler Decl. Ex. D at 775. Indeed, a pH value with no express or implied decimal places would not even be a *pH value*. It would just be an expression of an order of magnitude that has "no connection to the certainty of the value" of hydrogen ion concentration. Hensler Decl. Ex. B. at 541. The whole number just reflects the negative exponent in the base-ten logarithmic expression, but it would not represent a measured pH value. Abstractions like this are useless to a skilled artisan attempting to optimize the stability of a pharmaceutical product that is highly sensitive to differences in pH.

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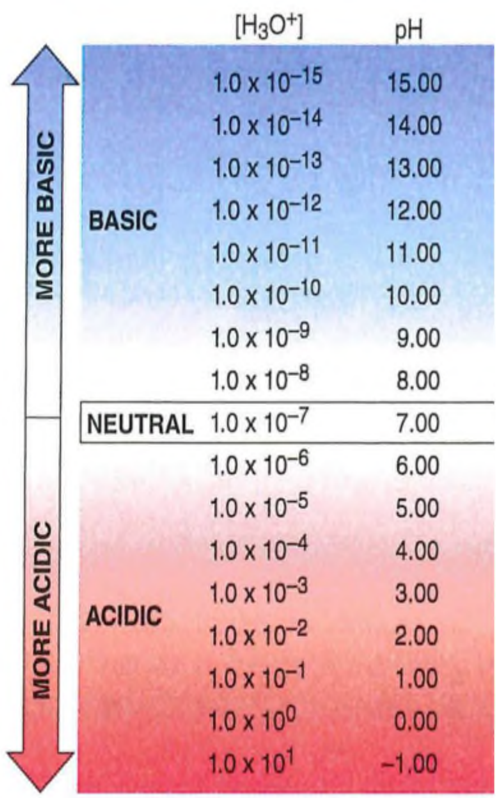
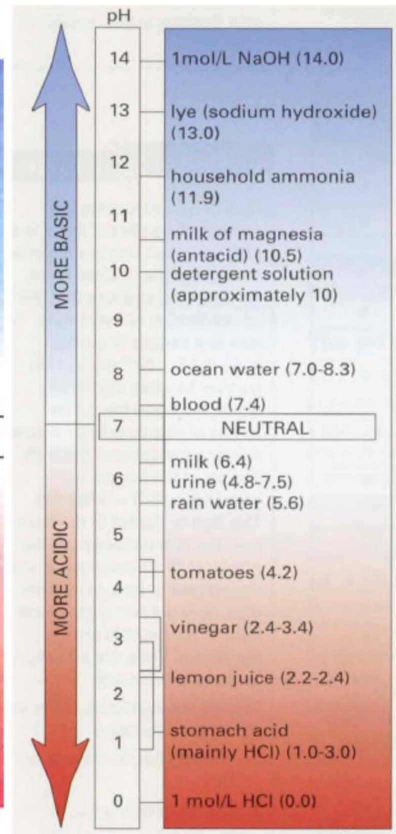
[8] The reason the numbers in scientific notation and pH are different (here, "2.7" versus ".57") is an artifact of the conversion from non-logarithmic to logarithmic expression using a calculator. This is not relevant to the claim construction, because the dispositive issue is not *what* digits those are—it is *how many* digits there *must be.*

[9] As these examples demonstrate, chemistry textbooks use "significant figures" and "significant digits" interchangeably. The principle is the same: "For measurements using logarithms, such as pH, the number of significant figures is equal to the number of digits to the right of the decimal, including all zeros. Digits to the left of the decimal are not included as significant figures since they only indicate the power of 10. *A pH of 2.45, therefore, contains two significant figures.*" Hensler Decl. Ex. E at 14 (emphasis added).

As the extrinsic evidence establishes, pH values as of the time of the priority date were routinely expressed to the tenth, hundredth, if not the thousandth, of the unit, even when displayed alongside single-digit whole numbers showing the pH *scale*:





Hensler Decl. Ex. D at 776; Hensler Decl. Ex. C at 388. Note that, in the second chart, the one reported value that does *not* have at least one decimal point (detergent solution) is qualified by the word "approximately"—*i.e.*, "approximately 10." The lack of certainty is explicitly intended in this measured value.

Just as often, particularly when a pH value is a whole number, skilled artisans will drop the trailing zeros and express pH as an integer. This does not mean, however, that the artisan intends to report pH at a level of abstraction equivalent to a bare order of magnitude. Consider the table below from Mustoe showing ion concentration values as raw numbers (column 2), exponential notation (column 3), and whole-number pH (column 5), all of them saying the exact same thing:

Table 10.7 Understanding pH

Range of acidity and basicity	$[H_3O^+]$ (mol/L)	Exponential notation (mol/L)	log	pH (-log $[H_3O^+]$)
strong acid	1	1×10^{0}	0	0
	0.1	1×10^{-1}	−1	1
	0.01	1×10^{-2}	−2	2
	0.001	1×10^{-3}	−3	3
	0.000 1	1×10^{-4}	−4	4
	0.000 01	1×10^{-5}	−5	5
	0.000 001	1×10^{-6}	−6	6
neutral $[H^+] = [OH^-] = 1.0 \times 10^{-7}$	0.000 000 1	1×10^{-7}	−7	7
	0.000 000 01	1×10^{-8}	−8	8
	0.000 000 001	1×10^{-9}	−9	9
	0.000 000 000 1	1×10^{-10}	−10	10
	0.000 000 000 01	1×10^{-11}	−11	11
	0.000 000 000 001	1×10^{-12}	−12	12
	0.000 000 000 000 1	1×10^{-13}	−13	13
strong base	0.000 000 000 000 01	1×10^{-14}	−14	14

Hensler Decl. Ex. C at 387. pH in column 5 is expressed in whole numbers. But there is always at least a "1" after the zeros in the raw concentration (column 2), and the base 10 exponent is always accompanied by a "1" figure in exponential notation (column 3). There is always a multiplier in front of the power of 10 (*i.e.*, 1.0 or 1). And the "1" is a significant figure. So, for pH "13," all of these expressions are identical:

	0.000 000 000 000 1	1×10^{-13}	−13	13

Id. Because there must always be at least the "1" multiplier for the exponential notation to reflect an underlying hydrogen concentration, "1 x 10^{-13}" is necessarily equivalent to a pH of 13.0. In "1 x 10^{-13}," the initial "1" is a significant figure. The number of significant figures in exponential notation is the same as the number of significant figures when expressed in pH. Hensler Decl. Ex. D at 774 ("5.4 x 10^{-4} M has two significant figures, so its negative logarithm, 3.27, has two digits to the right of the decimal point."). Therefore, "1 x 10^{-13}" is always the same as pH of "13.0."

For this reason, the chemistry textbooks of record pervasively use whole-number pH values *interchangeably* with pH values including one and sometimes *two* significant figures. In the Silberberg textbook, for example, a "neutral" pH is defined in all three ways:

7	NEUTRAL

Salt Solution (Examples)	pH
Neutral [NaCl, KBr, $Ba(NO_3)_2$]	7.0

pH of a neutral solution	= 7.00
pH of an acidic solution	< 7.00
pH of a basic solution	> 7.00

Hensler Decl. Ex. D at 775, 797. Indeed, the textbooks show whole-integer pH values imply at least one significant figure *even when comparing orders of magnitude*. Consider this passage from Kessel, which equates the terms "pH 3.0," "1 x 10^{-3}," and "pH 3":

> Note that the hydrogen ion concentration changes by a multiple of 10 for every increase or decrease of one pH unit. For example, at pH 4.0, $[H^+_{(aq)}]$ is 1×10^{-4} mol/L; at pH 3.0, $[H^+_{(aq)}]$ is 1×10^{-3} mol/L. At pH 3, the $H^+_{(aq)}$ concentration is ten times higher.

Hensler Decl. Ex. B at 541. A skilled artisan, in sum, understands that for a pH value to have practical significance, it must always have a significant figure, even when not written with one.

Finally, the extrinsic evidence demonstrates that skilled artisans understand at least one significant digit to the right of the decimal place is implied even when discussing ranges of pH value "greater than" or "less than" a certain whole-number pH. Mustoe, for example, observes:

> $[H_3O^+]$ in neutral water. The pH of the base is 11.00. All basic solutions have a pH that is greater than 7.

Hensler Decl. Ex. C at 387 (boxes added). On the following page, Mustoe provides a table showing that a "basic solution" has a pH "greater than 7.00"—so "greater than 7" and "greater than 7.00" are equivalent:

acidic solution	greater than 1×10^{-7}	$[H_3O^+] > [OH^-]$	< 7.00
neutral solution	1×10^{-7}	$[H_3O^+] = [OH^-]$	7.00
basic solution	less than 1×10^{-7}	$[H_3O^+] < [OH^-]$	> 7.00

Id. at 388 (boxes added). Under the conventions conveyed by Mustoe, then, a skilled artisan will understand “pH of 13 or higher” to refer to (1) a pH value of 13.00 and (2) a pH value higher than 13.00.

B. pH Meters as of the Priority Date Measured pH Down to Two (and Even Three) Digits, and Pharmaceutical Industry Standards Compel Such Precision.

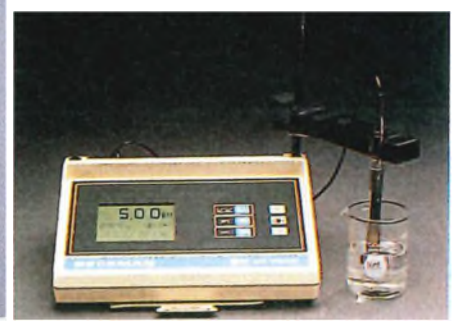
The skilled artisan’s understanding of pH values is further informed by the instruments used to measure them and industry standards for measuring pH related to pharmaceuticals.

First, the instrumentation. There are two principal ways to obtain pH values in a laboratory: “an acid-base indicator [*i.e.*, litmus paper] or, more precisely, with an instrument called a pH meter.” Hensler Decl. Ex. D at 777. Litmus paper is soaked in “a dye obtained from lichen” that turns red in response to an acid and blue in response to a base. Hensler Decl. Ex. B at 543. The resulting “color of the strip is compared with a color chart” to “estimate[]” pH. Hensler Decl. Ex. D at 777. Litmus paper is today more commonly used as a teaching tool in middle school, and for good reason: it is capable of only crudely measuring high-level approximations of pH values, as in the image below:

Id.

Litmus paper obviously cannot meet the needs of a skilled artisan working in a professional laboratory—particularly one preparing pharmaceutical drugs to meet the FDA's exacting safety and efficacy requirements. Hensler Decl. ¶¶ 38-39. A skilled artisan needs the precision and reliability of a pH meter, "an electronic instrument that measures the voltage between electrodes in a solution and displays this measurement as a pH value." Hensler Decl. Ex. B at 544; *see* Hensler Decl. ¶¶ 38-39. Unlike litmus paper, pH meters are capable of measuring pH with direct numerical precision—down to at least two decimal places (and thus two significant figures):





Hensler Decl. Ex. B at 544; Hensler Decl. Ex. C at 391; Hensler Decl. Ex. D at 777.

Indeed, a skilled artisan understands that the context of pharmaceutical science *compels* the use of precise instrumentation like these pH meters. A skilled artisan would be familiar with and rely on the United States Pharmacopeia (USP), a well-recognized standard in the pharmaceutical industry. Hensler Decl. ¶ 44 & Exs. F-G. USP sets science and quality standards for food, drug, and cosmetic products. Hensler Decl. ¶¶ 44-45. It provides a direct answer to the Federal Circuit's instruction to consider what "precision of measurement" a skilled artisan would expect: USP explains that, "[f]or compendium purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values ***to 0.02 pH*** unit." Hensler Decl. Ex. F (emphasis added). Thus a skilled artisan understands a pH meter *must* be capable of measuring to *at least* two decimal places/significant figures.

The Federal Circuit also suggested that the proper claim construction may require a "margin of error." All laboratory instruments will yield measurements that have some degree of imprecision, and pH meters are no different. For that reason, a margin of error may be needed to account for individual differences in machinery. Here, too, extrinsic evidence directly supports this point. The USP's 0.02-pH-unit standard of accuracy indicates a corresponding margin of error of 0.02 pH unit on either side of the measured pH. Hensler Decl. ¶ 49. Indeed, the U.S. National Institute of Standards and Technology (NIST)—a federal agency tasked with developing and promulgating standards for calibration and measurement—embraces an even narrower margin: Its reference standards "are considered to be accurate to ***±0.01 pH units***." Hensler Decl. ¶¶ 50-55 & Ex. J (emphasis added).

The extrinsic evidence thus demonstrates a skilled artisan will understand pH measurements to: (1) be precise down to the hundredth of the unit (the second decimal place); and (2) be measured with a margin of error of, at most, 0.02 (USP) pH units on either side. Those are the current industry standards—just as they were as of the priority date.

C. Applied to the '802 and '227 Patents, the Extrinsic Record Confirms that "a pH of 13 or higher" Is Bounded at the Lower End at a pH of Precisely 13, Which Cannot Round Down to 12.5.

Applying the above principles to the claim term "a pH of 13 or higher," the skilled artisan would understand the term to set a lower boundary at a pH of 13.00. To the extent a margin of error is needed to account for the accuracy limitations on a pH meter, that margin would only be ±0.02 pH. Understanding the pH measurement recited in the claim language to be precise down to the hundredth of a unit is consistent with the level of precision achievable by a basic pH meter at the time of the priority date. It is consistent with the level of precision commanded by the USP at that time. And it is consistent with the margin of error in pH measurements accepted by NIST. Nothing in the claim text, read in view of the extrinsic evidence, suggests that "a pH of 13 or

higher" refers to a bare integer that might round down to 12.5 under abstract principles of rounding. Indeed, that would provide a margin of 0.5 pH on either side—a "margin of error" *25 times greater* than the margin of pH measurement error suggested by USP, and *50 times greater* than that adopted by NIST. Nor, for that matter, does anything suggest that the term "pH of 13" refers to a bare power of ten conveying *no* precision. As noted, that would not be a pH value at all; it would not make sense in the context of patents for stable formulations of epoprostenol, a substance known to be highly sensitive to pH.

The specification and prosecution history reaffirm a reading with at least one implied significant figure and two decimal places of precision. The critical testing that ultimately supported approval of the patents appears in Example 4. The specification states that the inventors screened "formulations with the pH of bulk solution . . . adjusted between 10.5 and *13.0*." Dkt. 62-1 (10:62-64) (emphasis added). Table 8 displays those screened formulations, of which (among others) EPP-7, EPP-10, and EPP-13 are listed with the shorthand pH whole number of "13." But the March 20, 2006 provisional application recites the adjusted pH of these same EPP-7, EPP-10, and EPP-13 formulations as "*13.0*." Plainly, the necessarily implied significant figure of "0" was omitted.

Example 5, which reports results for reconstituted solutions, demonstrates the inventor could and did measure pH with a precision down to the hundredth of the unit, consistent with the principles reflected in the extrinsic record. Dkt. 62-1 (Tables 19-30). True, some samples are reported, as elsewhere, with pH to the tenth of the unit or with no decimal values at all. But, as noted above, skilled artisans occasionally drop trailing zeros on a pH value as shorthand or a matter of convenience. It is hardly a signal that the inventors intend to convey pH in the *claim* with no precision at all. To the contrary, as a matter of good science, the skilled artisan would understand

the inventor applied a consistent level of precision across all testing within Example 5—*i.e.*, at *least* to the tenth, but possibly to the hundredth, of a pH unit. Hensler Decl. ¶¶ 66-68.

II. Actelion's Alternative Construction, Intended to Capture pH Values as Low as 12.5, Is Not Supported by the Extrinsic Evidence or the Federal Circuit's Decision.

Mylan's proposed construction is abundantly supported by the record. By contrast, Actelion's construction—"12.5 to 13.4, or higher"—was not affirmed because, as the Federal Circuit recognized, it has no basis in the record. That construction remains untenable in light of the extrinsic evidence, whether based on the theory Actelion embraced on appeal or an alternative theory Actelion espoused below and may now seek to revive.

A. Actelion's Theory of Rounding the Abstract Integer "13" Is No Longer Viable.

In brief, Actelion's theory on appeal of significant-figure-based rounding cannot justify a construction of "12.5 to 13.4," because Actelion's textbooks conclusively refute it. Actelion embraced a claim construction based *solely* on the concept of "significant figures." According to Actelion, the claim term includes rounding to the ones place (the "3" in "13") because "a numerical value includes rounding based on the inventor's selection of significant figures in the claims where the intrinsic record does not indicate otherwise." 2023 WL 7289417, at *3. Only on that basis did Actelion advocate for a construction of "pH of 12.5 to 13.4, or higher." As the Federal Circuit recognized, however, Actelion's extrinsic evidence establishes that "pH of 13" *has* no significant figures unless there is a decimal point and a digit to the right. *See* 2023 WL 7289417 at *2. *See supra* Section I.A.

That evidence is fatal to the argument Actelion embraced on appeal, which was based entirely on the principle that "[s]cientific convention is to indicate the degree of rounding through the use of significant figures." Fed. Cir. Dkt. 18, at 13. Actelion nowhere suggested that it was "scientific convention" for a skilled artisan or anyone else to round based on the abstract notion of

"orders of magnitude." The "number of significant figures," Actelion added, "indicates which digits in a value should be rounded and which should not." *Id.* Actelion's urged "scientific convention," taken together with its extrinsic evidence, mean that Actelion's proposed claim construction of "12.5 to 13.4" is no longer viable. Such a construction would be based on the number of significant figures in the term "pH of 13" (without an implied .0, it has none), nor would it supply a reasonable "margin of error," as the Circuit recognized may be permitted by the term "pH of 13." 2023 WL 7289417 at *4. pH is not measured with a margin of error based on the digits to the *left* of the decimal. Hensler Decl. ¶¶ 70-74. The digits to the left represent an order of magnitude, a power of ten. Reading "pH of 13" to be "pH of 12.5 to 13.4" would therefore exceed any reasonable margin of *measurement error* supported by the record, radically expanding the claim scope beyond the range of pH values actually recited.

In short, because there are no significant figures in Actelion's understanding of "a pH of 13," there can be no rounding under the theory of the case Actelion urged on appeal. The Federal Circuit's decision therefore leaves two alternatives: (1) "pH of 13 or higher" refers to the range bounded at the bottom by *exactly* 13, with no approximation to account for measurement error; or (2) "pH of 13 or higher" refers to a range bounded at the bottom by 13, but with a *margin of error* based on the necessarily implied presence of a significant figure (*i.e.* bounded at the bottom by 12.98, using industry standards, or 12.95, using principles of rounding).

B. "pH of 13 or Higher" Does Not Refer to an Abstract Power of Ten and Does Not Imply Rounding Should be Applied to Integers in Exponents.

The theory Actelion pursued on appeal to capture a broader scope ("pH of *12.5* or higher") is no longer tenable. So Actelion may attempt to revive a convoluted theory it once pursued in the district court to reach the same result. This theory, based on applying rounding to abstract powers of ten, has no support in the extrinsic evidence or elsewhere. It holds that a skilled artisan would

read the claim term "pH of 13" as an "order of magnitude" equivalent to "10^{-13}," and apply principles of rounding to the nearest whole number in the exponent. In other words, a skilled artisan would know that exponents as low as "$10^{-12.5}$" round up to "10^{-13}" and so would conclude on that basis that the claim language encompasses pH as low as 12.5. The district court did not credit this convoluted theory the first time around, and for good reason: it is atextual, impermissibly abstract, and divorced from the subject matter of the patent. It is also inconsistent with the Federal Circuit's reasoning in remanding the case.

First, most obviously, this construction would require a skilled artisan to read a claim term as something that it is not. The claim states "pH of 13"—not "order of magnitude of 13" or "10^{-13}." The term "order of magnitude" does not appear anywhere in the claims or specification. The term "pH," though, appears dozens of times. Binding precedent has *rejected* just such an argument advocating a construction based on "orders of magnitude," finding it untethered to claim language and the patent as a whole. *U.S. Philips Corp. v. Iwasaki Electric Co.*, 505 F.3d 1371 (Fed. Cir. 2007). In *Philips*, the Federal Circuit dismissed the argument that "the term 'between 10^{-6} and 10^{-4} μmol/mm3' expresse[d] a range of orders of magnitude," because the patentee had not sought or obtained a claim with a "limitation refer[ring] to . . . a range, an order of magnitude, or an approximation." *Id.* at 1376. Instead, the Federal Circuit credited a construction of "1×10^{-6} and 1×10^{-4}." Adding the coefficient (the digit "1," or one significant figure) allowed the order of magnitude to have a comprehensible, measurable *meaning* to the skilled artisan, consistent with the concrete examples described in the specification. *Id.* Following the logic of *Philips* here would result in a construction of "pH of 13.0," because that is the logarithmic expression of "1×10^{-13}"—paralleling the "1×10^{-6}" and "1×10^{-4}" adopted in *Philips*.

Re-embracing this "powers-of-ten"/"order-of-magnitude"-based argument, moreover, would be an attempt to affirmatively *circumvent* the principle Actelion urged on appeal. *See* Fed. Cir. Dkt. 18, at 13. Actelion insisted it was ***black-letter*** Federal Circuit law that "the ordinary meaning of a claimed numerical value is determined by the number of significant figures." *Id.* at 29-30. Actelion is in a bind: it cannot concede "pH of 13" necessarily means "pH of 13.0" (it does; *see supra*) but cannot reach its desired result with rounding based on significant figures, because "pH of 13" would otherwise have none. Retreating to a "powers of ten" argument is the only way Actelion can argue that a pH value that *cannot* round actually *does* round after all, using a counterintuitive argument that would apply general rules of arithmetical rounding to exponents and not pH values.

Second, reading "pH of 13" to refer to an order of magnitude would make the claim construction impermissibly abstract. Actelion's position posits that a skilled artisan would automatically convert "pH of 13" into a negative exponent and conclude that values like $10^{-12.8}$ would round to 10^{-13}. "[T]he ordinary meaning of a claim term," however, "is not the meaning of the term in the abstract. . . . Instead, the 'ordinary meaning' of a claim term is its meaning to the ordinary artisan after reading the entire patent." *AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1330 (Fed. Cir. 2021) (quotation marks omitted). To be sure, a pH value is *derived* from an expression involving powers of ten. It incorporates a power of ten with whole number exponents only. But there is no support for the proposition that a skilled artisan reading the phrase "pH of 13 or higher" after reading the entire patent would flip a switch and start thinking like a mathematician.

Indeed, the sole evidence Actelion relied on for the proposition that "orders of magnitude" are subject to ordinary rounding rules underscores that this argument appeals to abstract theory,

not pharmaceutical practice. It is an introductory chapter concerning basic ways to understand numbers, taken from a physics (*not* chemistry) textbook. Ex. 2 at 1 ("Range of Magnitudes of Quantities in Our Universe").[10] The chapter explains that an order of magnitude "giv[es] an indication of size and not necessarily a very accurate value," which is why "when dealing with very big or very small numbers, scientists are more concerned with the order of magnitude of a measurement rather than the precise value." *Id.* "Order of magnitude, for all its uncertainty, is a good indicator of size." *Id.* at 2. And as an abstract matter, exponents can round. *See id.* But the *chemistry* textbooks of record nowhere suggest that skilled artisans would use "order-of-magnitude"-based exponential rounding. To the contrary, they invariably indicate that a pH value *without* a trailing significant figure is another way of stating a pH value *with* an implied significant figure of zero. *See supra* Section I.A. For example, Mustoe's comparative table shows that pH of 13 is synonymous with "1 x 10^{-13}"; expressed in pH, that is necessarily "13.0," with one significant figure. Hensler Decl. Ex. C at 387. Mustoe also equates pH of 7 to both "1 x 10^{-7}" *and* pH of 7.00. *Id.* at 387-388. Ordinary significant-figure-based rounding would apply to those measurements.

The extrinsic evidence, in short, cannot support a construction of "pH of 13" to refer to an order of magnitude that rounds based on digits expressed in exponents. A skilled artisan is not a student of physics interested in learning abstract ways to understand large numbers. Nor would a skilled artisan refer to the claim language for an inherently "uncertain[]" "indicator of size." Ex. 2 at 2. He is a chemist who, in the context of the patent as a whole, will read "pH of 13" to refer to what specific, reasonably measurable pH values are claimed. This patent, after all, is directed to stabilized pharmaceutical formulations tied to specifically measured pH values. The extrinsic

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[10] Greg Kerr & Paul Ruth, PHYSICS (3th ed. 2008), previously submitted as Exhibit 14 to Actelion's Opening Claim Construction Brief (Dkt. 63).

evidence confirms that the correct construction is one that incorporates a skilled artisan's practical understanding that "a pH of 13 or higher" is synonymous with "a pH of 1 x 10^{-13} or higher," and therefore with "pH of 13.0 or higher." It implicitly carries at least one significant figure (*i.e.*, 13.0).

Finally, an argument based on "orders of magnitude" cannot be squared with the Federal Circuit's reasoning in remanding the case. The Circuit recognized that a construction allowing rounding might be permissible, but only to provide a "margin of error" for the "measurement of pH value." 2023 WL 7289417 at *4. Specifically, "a margin of error for a pH of 13." *Id.* at *3. The claim, in other words, might allow a skilled artisan to attempt to hit a pH of 13, but slightly miss the target within the bounds of expected experimental or instrument error. It is impossible to square this with a "12.5 to 13.4" construction based on "orders of magnitude." A skilled artisan cannot measure an order of magnitude or a power of ten—only a pH. He uses a pH meter to do so. And, as the extrinsic evidence shows, pH meters measure exact pH values down to the second decimal place. Even applying ordinary rounding rules, the widest margin of error reasonably supported by the record is 12.95 to 13.04.

CONCLUSION

Mylan respectfully requests the Court construe the claim "pH of 13 or higher" as (1) "a pH of 13, but not less than 13, or higher," such that any pH values below 13 are not included; or, in the alternative, as (2) encompassing a margin of error based on the necessarily implied significant figure: "a pH of 12.98 or higher," consistent with industry standards, or "a pH of 12.95 or higher," consistent with principles of significant-figure-based rounding.

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CERTIFICATE OF SERVICE

I hereby certify that on this the 21st day of November 2023, I electronically filed the foregoing "DEFENDANT MYLAN PHARMACEUTICALS INC.'S POST APPEAL CLAIM CONSTRUCTION BRIEF REGARDING EXTRINSIC EVIDENCE" with the Clerk of the Court using the CM/ECF system, which will send electronic notification of the same to all counsel of record.

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